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Abstract and Review of "Studien Über Vererbung und Entstehung Geistiger Störungen. I. Zur Vererbung und Neuentstehung der Dementia praecox." (Studies on the Inheritance and Origin of Mental Illness: I. To the Problem of the Inheritance and Primary Origin of Dementia Praecox.)*

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The first major family study of schizophrenia, reported by Ernst Rüdin in 1916, examined 2,732 siblings of 755 probands, diagnosed according to the teachings of Kraepelin. This study, the goal of which was to see whether the segregation pattern of schizophrenia in siblings conformed to simple mendelian expectations, was the first in psychiatry to use systematic ascertainment, proband correction and calculation of an age corrected risk of illness—the morbid risk (MR). The MR for narrowly and broadly defined schizophrenia in this sample can be calculated to equal 5.4 and 7.7%. "Other psychoses"—a heterogeneous category—were also common in these siblings (a MR of 5.1%). In a small sample of half-siblings, the MR for narrowly defined schizophrenia was quite low (0.6%). The risk for schizophrenia in siblings was significantly increased by a parental diagnosis of alcoholism, a history of schizophrenia in second or third degree relatives, and, particularly, by a parental diagnosis of "other psychoses." No evidence was found for sex-specific transmission of schizophrenia in these sibships. The MR for narrowly and broadly definite schizophrenia in parents of these probands can be estimated to be 2.3% and 3.9%, respectively. In accord with more recent studies, Rüdin found i) a familial relationship between schizophrenia and other psychoses ii) a substantially lower risk for schizophrenia in parents vs. siblings and iii) a segregation pattern of schizophrenia in siblings that did not conform to that expected for a simple mendelian disorder.

KEY WORDS: psychiatry history, psychiatric genetics, schizophrenia

METHODS

Probands were patients with a definite diagnosis of Dementia Praecox from the Psychiatric Department of the "Hospital of the Left Bank of the River Isar," for the years 1898–1904, and its successor, the Munich Psychiatric University Clinic, from 1904 on. Most of the probands appear to have come from the University Clinic. Although this is not explicitly stated, these cases probably represented most, if not all, admissions with this diagnosis. The period of time over which these cases were gathered is not completely clear. Rüdin probably began collection in 1907 when he came to Munich and concluded collection in 1911. Proband ascertainment could not have practically continued beyond 1913 since the completed manuscript was sent to the publisher in May 1914. Publication, however, was delayed because of World War I. Finally, a small number of cases were referred to Rüdin from the old Provincial Mental Hospital of Munich (located in the nearby village of Eglfing) by Kraepelin, Vocke, and Rehm. It would appear that at most 33 cases came from Eglfing and 668 from the Psychiatric University Clinic or the "Isar" Hospital. In all cases, probands were accepted only on the basis of the certainty of their diagnosis and never because of their family history. Such systematic ascertainment was in fact, very unusual at that time, when most pub-

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As this paper abstracts, reanalyzes and interprets upon the original article by E. Rüdin, it is not a translation, and hence E. Rüdin's name is not listed as author.

*"Monographien aus dem Gesamtgebiete der Neurologie und Psychiatrie," Number 12, Springer, Berlin, 1916 by Ernst Rüdin.

lications in Psychiatric Genetics presented cases with particularly strong family loading, concordant twin pairs, or from other "interesting families." This monograph also presents data on 34 affected parent-offspring pairs, but these are analyzed separately from the main group of probands.

Diagnostic Approach

At the Munich clinic, where the large majority of the probands were ascertained, nearly all diagnoses would have been reviewed by Kraepelin personally. At the other institutions where probands were ascertained ("Isar" and Eglfing hospitals), diagnoses would certainly have been made in accordance with Kraepelin's views. At the time this work was done, Kraepelin had split off from dementia praecox his group of paraphrenias, which consisted of non-deteriorating paranoid-hallucinatory syndromes, often presenting with quite bizarre delusions [Kraepelin, 1971]. Many such cases would probably be described as relatively good-outcome paranoid schizophrenics by modern criteria. Rüdin followed Kraepelin's approach and excluded all cases of paraphrenia from the present series.

The criteria for the diagnosis of dementia praecox are not specifically outlined in this monograph. However, Rüdin did describe "syndromal occurrence of several main symptoms with other clues." "Main symptoms" were flattened affect, defect of volition, loosening of associations (literally "cognitive disturbances in the sense of Bleuler"), "intrapsychic ataxia," early onset, and failure to recover ad integrum. Rüdin did accept as probands cases with late onset or recovery if other key symptoms were present. What Rüdin meant by "other clues" is not clear, but probably these referred to social/occupational consequences of illness. Rüdin attempted to follow-up all the probands of his series so that diagnoses were made, in nearly all cases, on the basis of both cross-sectional and longitudinal data. At follow-up, cases with an incorrect or uncertain diagnosis were eliminated. We can conclude with considerable confidence that Rüdin's diagnostic approach to schizophrenia was a narrow one and would not include cases with brief reactive or atypical psychosis, delusional disorder, or schizophrenia spectrum personality disorder.

Rüdin applied the same criteria for dementia praecox to relatives as to probands. For a certain diagnosis of dementia praecox in relatives, reliance was placed only on hospital records, direct observation by Rüdin himself or "precise description" by other outside observers. Rüdin specifically expressed concern about the reliability of diagnoses and case histories from other hospitals and earlier time periods. He concludes that they are usually useful and, in the absence of other information, can be relied upon.

While Rüdin had a narrow view of dementia praecox, he had a quite broad view of what he terms "other psychoses." In addition to manic-depressive, paranoid, hysterical, and other "functional" psychoses, Rüdin included in this category organic psychoses (e.g., those associated with epilepsy, thyroid disease, dementia, and tertiary syphilis), severe mental retardation, and hospitalized cases of "psychopathy" or personality disorder.

Sources of Information

For both relatives and probands at follow-up, Rüdin tried to gain first-hand information, either by interview or by letter. No information is given on how many relatives or probands were contacted in this way. In addition to personal contact, and what would now be termed "family history information" obtained from other relatives, Rüdin used a wide variety of other sources of information including marriage license bureaus, parish registries, official records of estates, divorce and guardianship, case histories from clinics, family pedigrees, and records from the police, prisons, and the military. Each proband-family had a file, containing all available information, including a detailed pedigree. A standard card was also filled out for every proband (illustrated in Rüdin's table 8).

Rüdin used several age correction methods, including the Abridged Weinberg with varying periods of risk (including 13–36, 17–35, and 14–40), methods dividing the risk period into three or more categories and what he terms the "individual morbidity table" (Table 20), which appears to be an early form of the life table method.

Several of Rüdin's probands came from the same family. To correct for this multiple ascertainment, Rüdin explicitly used the Weinberg proband method and, in fact, illustrates the results obtained with and without this method. Its application in psychiatric genetics was very new at the time this monograph was written [Weinberg, 1903, 1908, 1913].

RESULTS

The main focus of Rüdin's monograph was on the pattern of illness in siblings of the probands. He divided his results in siblings into those with and without an affected parent. Rüdin had 721 systematically ascertained probands from 701 sibships where both parents were free of dementia praecox. It was possible to calculate the sex ratio for this group of Rüdin's probands; there was a modest male preponderance (402 male, 319 female for a ratio of 1.29:1.00).

There is some uncertainty as to the total number of co-siblings of these probands who survived to the beginning of their 14th year of life, as both 2,442 and 2,600 are mentioned. We consider the latter figure to be more likely correct when using Weinberg's proband method. The lower number may reflect the number of siblings uncorrected for ascertainment.

Eighty-five of the cosiblings were affected with schizophrenia, for a lifetime prevalence of 3.27% (although in certain parts of the monograph it can be calculated that Rüdin assumed 86 affected co-sibs). Of these 2,600 co-siblings, 2,020 were under age 40 and 580 were aged 40 and above. By the Abridged Weinberg method [Weinberg, 1903, 1908], Rüdin calculates 1,590 lifetimes at risk for a morbid risk (MR) for dementia praecox of 5.35 $\pm$ 0.56%. Using several other age-correction methods, including an early form of the lifetable method, he arrives at slightly lower MRs, from 4.48 to 4.83%.

Thirty-four of Rüdin's probands had one parent with definite dementia praecox. These all came from differ-

ent families. These 34 families contained 132 co-sibs of probands and 3 secondary cases of dementia praecox, for an uncorrected lifetime prevalence of 2.27%. However, these sibships were on average younger than those from dementia praecox-free parents, and the lifetimes at risk in the sibships, by the abridged Weinberg method, was only 48.5, for a MR of schizophrenia of 6.19 ± 3.46%, which is slightly but non-significantly higher than the risk in siblings where the parents were free of dementia praecox. It is possible to combine the results from these two series (probands without and with an affected parent): 755 schizophrenic probands had siblings with 1638.5 lifetimes at risk; 88 secondary cases of schizophrenia were found, producing a MR for schizophrenia of 5.37 ± 0.56%.

Rüdin also examined in detail results for "other psychoses" in siblings of probands. As noted above, this was a very heterogeneous group. Rüdin reported 79 cases of "other psychoses" in the 2,600 co-siblings of schizophrenic probands with no parent affected with dementia praecox, for a prevalence of 3.04 ± 0.34%. Using the early lifetable method, he reports a MR for "other psychoses" of 4.12%. The Abridged Weinberg method applied to this same data yields a MR of 4.97%. In the 132 co-siblings of schizophrenic probands with a parent affected with dementia praecox, Rüdin found five cases of "other psychoses," for a MR of 10.31 ± 4.37%. Combining both these groups, we can calculate that the risk for "other psychoses" in the co-siblings of all of Rüdin's probands was 5.12 ± 0.54%, very similar to the risk found for schizophrenia.

At the end of his monograph, Rüdin reports the probable diagnosis of these 79 cases of "other psychoses" in the siblings of schizophrenic probands with unaffected parents. In 43 of these, case histories were available. We summarize his table, including Rüdin's estimate of how many of these cases probably had dementia praecox:

Diagnosis	N	Probable or possible *dementia* praecox
Dementia praecox	6	6
Atypical manic depressive vs. dementia praecox	8	8?
Mental retardation/idiocy	8	3
Organic psychoses[a]	7	1?
Severe hospitalized "psychopathy"	5	2?
Epilepsy	3	
"Paranoid disturbances"	2	1?
Psychogenic psychosis and hysteria	2	
Manic depressive	1	
"Twilight state" ?epilepsy vs. hysteria	1	1?
TOTAL	43	9 prob/13 poss

[a] Poliomyelitis, 2; syphilitic general paralysis, 2; Grave's disease, 1; other, 2.

Rüdin did not count these 13 cases of possible dementia praecox in siblings in his main analysis because he did not consider their diagnosis to be beyond doubt.

The 36 cases of "other psychoses" in siblings without complete case histories (only short descriptions were available) were tentatively diagnosed by Rüdin as follows:

Diagnosis	N	Possible dementia praecox
Unusual periodic or depressive states	11	4
Unknown psychosis	11	6
Epilepsy	3	
Hysteria	3	
Suicide	2	
Senile dementia-arteriosclerotic	2	
Severe psychopathy	2	1
Psychosis after pneumonia	1	1
Mental retardation and psychosis	1	1
Total	36	13

Thus, of the total 79 cases, 35 or 44.3% were considered by Rüdin to be possible or probable cases of dementia praecox. The remaining 44 cases can be roughly and usefully divided into 19 cases where the psychosis was probably the result of coarse brain disease (mental retardation, organic psychoses, senile dementia, or epilepsy) and 25 cases where it was not (e.g., "functional" psychosis).

The MR for broadly defined (definite, probable, or possible) dementia praecox in the siblings with no parents affected can be calculated to be 120/1,590 = 7.55 ± 0.66%. Adding to this the 25 cases of "functional" psychosis in siblings, a MR for all cases of non-organic psychosis would be 145/1,590 = 9.12 ± 0.72%.

Rüdin identified five cases of other psychoses among the siblings of dementia praecox probands with a parent affected with dementia praecox. Of these five, all of whom probably had a "functional" psychosis, Rüdin considered three to have possible dementia praecox. Therefore, the MR for broadly defined dementia praecox in the siblings of all of Rüdin's probands (i.e., those with and without an affected parent) can be calculated to be 126/1,638.5 = 7.69 ± 0.66%. The MR for "functional psychosis" in the siblings of the complete proband series is 153/1,638.5 = 9.33 ± 0.72%.

Risk to Siblings as a Function of the Psychiatric Status of the Parents

Rüdin extensively analyzed the risk to siblings of schizophrenic probands as a function of alcoholism or "other psychoses" in parents and as a function of the presence or absence of dementia praecox in relatives of the parents.

Alcoholism

Using the Abridged Weinberg method, Rüdin found that the risk for dementia praecox in siblings of probands when one parent was alcoholic, but not otherwise mentally ill, and the other parent was not mentally ill (21/269 = 7.81 ± 1.64%) was significantly greater than that found in the remaining co-siblings (64/1321 = 4.84 ± 0.59%) ($\chi^2 = 3.87$, $P = 0.05$).

Other Psychoses

Rüdin examined the risk for dementia praecox in siblings of schizophrenic probands as a function of the

presence or absence of "psychoses other than dementia praecox" in one or both parents. As above, the term "psychoses" was used here by Rüdin more broadly than it would be today and included cases of hysteria, severe psychopathy, and probably dementia. From his tables, it is possible to reconstruct, at least approximately, the following MRs using the Abridged Weinberg method: both parents with a "psychosis other than dementia praecox," 5/22 = 22.73 ± 8.93%; one parent with a "psychosis other than dementia praecox," 27/328.5 = 8.22 ± 1.52%; neither parent with a "psychosis other than dementia praecox," 53/1239.5 = 4.28 ± 0.57%. These risks are highly significantly different from one another (χ^2 = 21.28, df = 2, P = 0.00002), providing further support for a familial relationship between narrowly defined dementia praecox and more broadly defined psychoses.

Dementia Praecox in Other Relatives

Rüdin found that the risk for dementia praecox in siblings of schizophrenic probands when parents were free of identifiable mental illness or alcoholism but where dementia praecox was found in other relatives (e.g., uncles, aunts, or cousins of the proband) was, by the Abridged Weinberg method, 13/159 = 8.18 ± 2.18%. Rüdin does not present results for the proper comparison group (siblings of probands where both parents were free of any mental illness or alcoholism but no cases of dementia praecox were found in any relatives). However, given that this risk is significantly greater than in the most appropriate available comparison group (risk to siblings where both parents are free of other psychoses, 4.28%) (χ^2 = 4.76, df = 1, P = 0.03), it is probable that the presence of cases of dementia praecox in second-and third-degree relatives of probands conveyed a significantly increased risk of illness in siblings.

Gender Effects

As noted above, Rüdin's proband sample had a modest male preponderance (1.26:1). The gender ratio in all siblings (affected and unaffected) revealed a very slight male excess (1.04:1). Rüdin's approach to calculating the sex ratio in affected siblings was confusing. In the secondary cases of dementia praecox who were not themselves probands, there was a quite substantial male excess (29 male vs. 15 female cases for a ratio of 1.93:1). This is significantly different from chance expectation (χ^2 = 3.92, df = 1, P = 0.05). Rüdin suggested three possible explanations for this apparent anomaly: i) diagnosis of dementia praecox is more difficult in females than males, as in females dementia praecox may be more often misdiagnosed as manic-depressive illness or hysteria; ii) men are hospitalized, and hence come to psychiatric attention, more often than females because of an inability to earn a living or because of violent behavior; and iii) dementia praecox is truly more common in men than in women.

However, to properly calculate the sex ratio of secondary cases of dementia praecox, secondary cases who were themselves probands (and were ascertained through another proband in the family) should also probably be included. In this group, the gender ratio (22 male vs. 20 female cases: 1.10:1) is quite close to unity. (This is one situation where the total number of affected co-sibs 29+15+22+20 sums to 86 rather than 85). In all 86 affected co-sibs, then, the ratio of males to females is 51:35 or 1.45:1 which is not significantly different from chance expectations (χ^2 = 2.39, df = 1, NS).

Rüdin presented data which allow an examination of sex-specific transmission of dementia praecox in affected sibling pairs. Forty-six siblings of male probands themselves had schizophrenia, of whom twenty-nine were male and seventeen female. Forty siblings of female probands were diagnosed as schizophrenia, of whom twenty-two were male and eighteen female. Applying a χ^2 test to this 2 × 2 table, the pattern of findings does not differ from that expected by chance (χ^2 = 0.57, df = 1, NS).

Half-Siblings

Rüdin ascertained a total of 498 half siblings of schizophrenic probands. This was quite a young sample and yielded, using the Abridged Weinberg method, only 175.5 lifetimes at risk. Only one case of definite dementia praecox and three of other psychoses were found in these half siblings. The MR for dementia praecox, other psychoses, and total psychoses in half siblings can be calculated as 0.56 ± 0.56, 1.70 ± 0.98, and 2.27 ± 1.12, respectively. Although examined by Rüdin, the sample of half sibs sharing with the proband a parent with dementia praecox was too small to meaningfully analyze (five families with one grown-up half-sib).

Parents

Rüdin does not extensively analyze the risk for dementia praecox in parents of his dementia praecox probands. He notes that there are 34 definite, 11 probable, and 14 possible cases of dementia praecox in these parents. Rüdin does not present MR for dementia praecox in parents, but we can calculate a lower limit for these risks, assuming that all parents had completed their age at risk. The estimated MR for definite dementia praecox in parents is 34/1,510 = 2.25±0.38%. Adding the probable and possible cases increases the MR to 59/1,510 = 3.91 ± 0.50.

Remainder of Monograph

Rüdin goes on to examine several other issues relating to the etiology of dementia praecox. He examines in considerable detail the influence of birth order and "anteposition" in dementia praecox (the tendency for age of onset to be younger in offspring than in parents and in younger vs. older siblings). He discusses the possible Mendelian basis for dementia praecox. He notes that simple monogenic hypotheses are incompatible with the evidence. He notes both earlier in the monograph and in the conclusion that both "internal milieu" (e.g., other genetic factors) and "external milieu" (e.g., environmental factors) almost certainly play an etiologic role in dementia praecox. He does propose a possible two-locus recessive model which, with rare allele frequencies, would predict a MR in siblings approaching 6.25%. He also discusses "polymorphic inheritance," recognizing that the coincidence of dementia praecox and other psychoses in his families cannot be due to chance. He

considers whether this could be due to "selective mating," exogenous factors, or a true genetic/etiologic *relationship* between dementia praecox and these other psychoses. He proposes that the basis of these other psychotic disorders may be other "gene combinations" within his two locus model. Although he does not specifically address issues of what would now be termed schizophrenia spectrum personality disorders, several passages indicate that Rüdin was aware of the probability that a full genetic endowment for dementia praecox might, in some individuals, remain latent or "mute."

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